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## TELEFAX

Date: February 23, 2006

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Our Docket No. YU 132

Client/Matter No: 078245-00045

Your Docket No.

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### MESSAGE:

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Peter M. Glazer

Serial No: 09/978,333

Art Unit: 1634

Filed: October 15, 2001

Examiner: Carla Myers

For: *TRIPLE-HELIX FORMING OLIGONUCLEOTIDES FOR TARGETED  
MUTAGENESIS*

#### Attachments:

Transmittal Form PTO/SB/21;

Fee Transmittal PTO/SB/17;

Reply Brief; and

Request for Oral Hearing

(45058774.1)


FEB 23 2006

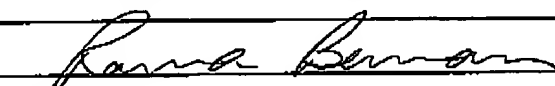
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<b>TRANSMITTAL FORM</b>  (to be used for all correspondence after initial filing)	Application Number	09/978,333
	Filing Date	October 15, 2001
	First Named Inventor	Peter M. Glazer
	Art Unit	1634
	Examiner Name	Carla Myers
Total Number of Pages in This Submission	Attorney Docket Number	YU 132

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/Declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation <input type="checkbox"/> Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Request for Oral Hearing
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Date	February 23, 2006	Reg. No. 31,284

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Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).**FEE TRANSMITTAL**  
**For FY 2005**☒ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$ 500)**Complete if Known**

Application Number	09/978,333
Filing Date	October 15, 2001
First Named Inventor	Peter M. Glazer
Examiner Name	Carla Myers
Art Unit	1634
Attorney Docket No.	YU 132

**METHOD OF PAYMENT** (check all that apply)

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**FEE CALCULATION****1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

**2. EXCESS CLAIM FEES**

Fee Description	Fee (\$)	Small Entity Fee (\$)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)	Multiple Dependent Claims	Fee (\$)	Fee Paid (\$)
17 - 25 or HP =	x	0.00	= 0.00			
HP = highest number of total claims paid for, if greater than 20						
Indep. Claims	Extra Claims	Fee (\$)	Fee Paid (\$)			
1 - 3 or HP =	0	x 0.00	= 0.00			
HP = highest number of independent claims paid for, if greater than 3						

**3. APPLICATION SIZE FEE**

If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
- 100 =	/ 50 =	(round up to a whole number) x	=	

**4. OTHER FEE(S)**

Non-English Specification, \$130 fee (no small entity discount)

Other: Request for Oral Hearing

Fees Paid (\$)

\$500.00

**SUBMITTED BY**

Signature	Registration No. 31,284	Telephone (404) 879-2151
Name (Print/Type) Patrea L. Pabst	(Attorney/Agent)	Date February 3 2006

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Peter M. Glazer

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Art Unit: 1634

FEB 23 2006

Filed: October 15, 2001

Examiner: Carla Myers

For: *TRIPLE-HELIX FORMING OLIGONUCLEOTIDES FOR TARGETED  
MUTAGENESIS*Mail Stop Appeal Brief-Patents  
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## REPLY BRIEF

Sir:

This is a Reply Brief to the Examiner's Answer mailed December 23, 2005, in the above-identified patent application. Submitted with this Reply Brief is a Request for Oral Hearing. The Commissioner is hereby authorized to charge \$500, the fee for a Request for Oral Hearing for a small entity, to Deposit Account No. 50-3129. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

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**(1) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL**

The issues now present on appeal are:

(1) whether claims 7-12 and 15-25 are enabled as required by 35 U.S.C. § 112, first paragraph.

(2) whether claims 7-12 and 25 are novel as required by 35 U.S.C. § 102(b) over Chan, et al., *Journal of Biological Chemistry* 274:11541-11548 (1999) ("Chan").

Appellant appreciates the withdrawal by the Examiner of the rejection of claims 15-24 under 35 U.S.C. § 112, second paragraph, the rejection of claims 15-21 and 23-24 under 35 U.S.C. § 102(b) as anticipated by Chan and the rejection of claim 22 under 25 U.S.C. § 103(a) as being obvious in view of Chan.

**(2) ARGUMENTS**

Appellant affirms all of the arguments made in the Appeal Brief.

**(i) Rejection under 35 U.S.C. § 112, first paragraph**

To comply with 35 U.S.C. § 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). However, this is what the Examiner wants. The crux of the Examiner's argument is that the Examiner thinks that the claims are allegedly not enabled because the Appellant has not demonstrated therapeutic efficacy. However, the claims do not require therapeutic efficacy. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of

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the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). As set forth in *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables any mode of making and using the invention." These requirements have clearly been met by the Appellant.

***Claims 7-12 are enabled***

Independent claim 7 defines a method for targeted recombination of a nucleic acid molecule comprising the steps of: a) providing a single-stranded oligonucleotide having a sequence that forms a triple-stranded nucleic acid molecule by hybridizing with a target sequence in a double-stranded nucleic acid molecule with a  $K_d$  of less than or equal to  $2 \times 10^{-7}$ ; and b) providing a donor nucleic acid such that recombination of the donor nucleic acid into the target sequence is induced by triple helix formation between the single-stranded oligonucleotide and the double-stranded nucleic acid molecule. Nowhere in this claim or the dependent claims are limitations concerning therapeutic efficacy.

The components required by the claims include a single-stranded oligonucleotide that forms a triple-stranded nucleic acid molecule and a donor nucleic acid. Single-stranded oligonucleotides that form a triple-stranded nucleic acid molecule (or TFOs) are described in the specification at least at page 7 to page 11. TFOs were well known to one of skill in the art at the time of filing the present application (see at least page 2, lines 1-5). Furthermore, the specification spells out in detail that such oligonucleotides can be synthetic or isolated, are preferably 10 to 60 nucleotides in length and should have a low dissociation constant ( $K_d$ ). Not

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only does the specification describe suitable dissociation constants for TFOs (such as those required by the claims), the specification also describes methods for determining the dissociation constant of an oligonucleotide/target pair.

Donor nucleic acids are described in the specification at least at page 9, lines 11-28 and page 14, lines 8-25. The donor nucleic acid can be tethered or un-linked to the single stranded oligonucleotide as described in the specification at least at page 17, lines 19-26.

The claims define methods for targeted recombination of a nucleic acid molecule comprising administration of a TFO and a donor nucleic acid molecule. There is no dispute that the claims are enabled for *in vitro* and *ex vivo* methods. The Examiner's arguments focus on the fact that the claims are allegedly not enabled for *in vivo* methods. However, all that is required to practice the method as defined by the claims is (1) provision of a suitable TFO and donor nucleic acid and (2) injection of the TFO and donor nucleic acid. As described above and in the Appeal Brief, the specification enables one of skill in the art to make and use suitable TFO and donor nucleic acids. Therefore, all one of skill in the art must do to perform the methods defined by the claims *in vivo* is inject them. The Examiner has provided no evidence to support her arguments that the claims are not enabled. As discussed above, the Examiner is arguing that Appellant should demonstrate therapeutic efficacy. ***This is not the legal requirement when the claims do not require therapeutic efficacy.***

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). In this case, it is clear that those skilled in the art engage in *in vivo* methods. Methods for

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insertion of a homologous DNA sequence or DNA fragment *in vivo* and methods of targeting TFOs to a specific site in the genome were known to one of ordinary skill at the time of filing the present application. As described in detail in the Appeal Brief, one of ordinary skill in the art would expect that a TFO injected into an animal would result in site-directed mutagenesis as predicted by the *in vitro* data. Indeed this is exactly what Appellant demonstrates in Examples 6 and 7: injection of the TFO resulted in site-directed mutagenesis *in vivo* as predicted from the *in vitro* data. There has been no evidence provided by the examiner that the evidence in the specification would not be predictive of an oligonucleotide which further included a donor nucleic acid. The Examiner merely argues that the mutations are not sufficient for *therapeutic* efficacy. However, the evidence in the specification clearly demonstrates efficacy in a cell system which was predictive of the actual efficacy in animals. *There is no legal requirement for enablement of a certain amount of efficacy*; all that is required is that the specification (coupled with what is known in the art) provides one of ordinary skill with the ability to make and use the method defined by the claims without undue experimentation. This Appellant has done.

Furthermore, Appellant has provided working examples for the oligonucleotides linked or unlinked to a donor nucleic acid using both cell-free and cell systems (see Examples 2-4 in the specification at pages 27-31). Absent some evidence otherwise, one skilled in the art would expect the oligonucleotides, linked or unlinked to a donor nucleic acid, to promote targeted recombination in animals as in the cell systems, based on the evidence in the specification. One of ordinary skill in the art would expect that injection of nucleic acid molecules as defined by the claims into an animal would result in distribution of the nucleic acid molecules to tissues and cell

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nuclei, thereby resulting in targeted recombination of a donor nucleic acid into a target DNA sequence. Therefore, it would not require undue experimentation to practice the method for targeted recombination *in vivo* as defined by claims 7-12.

***Claims 15-25 are enabled***

Dependent claims 15-25 specify that the method of claim 7 is carried out to produce changes in the genome of an intact human or animal. As discussed in the Appeal Brief, studies have established that DNA molecules can be administered by i.p. or intravenous injections and will gain access to tissues and cell nuclei. As expected from these studies, Appellant demonstrated that chromosomal DNA throughout the somatic tissues of an animal can be targeted by nucleic acids, which is described in the specification at least at examples 6 and 7, pages 31-35. Since *in vivo* distribution of nucleic acids is achieved by injection of nucleic acids and all that is required to practice the method as defined by the claims is injection of a TFO linked or unlinked to a donor nucleic acid, it is clear that the quantity of experimentation required to practice the claimed method is minimal. It is also clear from the amount of guidance provided in the specification as discussed above that the amount of experimentation required to practice the claimed method is not undue.

**(ii) Rejection Under 35 U.S.C. § 102**

***Chan***

The Examiner has only maintained his rejection of claims 7-12 and 25 under 35 U.S.C. § 102(b) as anticipated by Chan. However, as discussed thoroughly in the Appeal Brief, Chan is not prior art as the present application is entitled to a priority date of 1995. The discussion below

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refers to U.S. Patent No. 6,303,376 ("the '376 patent") and U.S. Patent No. 5,962,426 ("the '426 patent"). A discussion of the relationship between the '376 and '426 patents and the present application was provided in the appeal brief.

With respect to claims 7-12, the Examiner argues that the '376 and '426 patents do not support conception of (1) a  $K_d$  of less than or equal to  $2 \times 10^{-7}$ , (2) TFOs having a length between 10 and 60 nucleotides, and (3) a TFO that is tethered or untethered to a donor nucleic acid. With respect to claims 12 and 25, the Examiner argues that the '376 and '426 patents do not support a donor nucleic acid at least 30 nucleotides in length or between 10 and 40 nucleotides in length.

In response to Appellant's Appeal Brief, the Examiner argues that a claim as a whole is assigned an effective filing date rather than the subject matter within a claim being assigned individual effective filing dates. However, the Examiner lumps claims 7-12 together during her arguments and does not examine each claim individually. It should be noted that element (2) is only recited in claim 8. Moreover, element (2) is recited in claim 16, which is allowed.

It has been well established that a patent need not teach, and preferably omits, what is well known in the art. *Hybritech Incorporated v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Furthermore, "the meaning of equivalents is well understood in patent law, and an applicant need not describe in his specification the full range of equivalents of his invention" (citation omitted). *Noll*, 545 F.2d at 149-50, 191 USPQ at 727.

TFOs and methods of making and using TFOs were well known to one of skill in the art as described in the '376 patent at least at column 1, line 24 to column 2, line 10. The '376 patent

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also discloses at least at column 4, lines 55-64 that the conditions under which a triple-stranded structure will form are standard assay conditions for *in vitro* mutagenesis and physiological conditions for *in vivo* mutagenesis. The '376 patent defines exemplary suitable dissociation constants ( $K_d$ ) at least at column 5, lines 3-4, and at column 9, lines 25-56, and at Table 1.

Specifically, Table 1 states that AG20 has a  $K_d$  of  $3 \times 10^{-7}$  and AG 30 has a  $K_d$  of  $2 \times 10^{-8}$ .

These results in Table 1 demonstrate that TFOs with  $K_d$ 's of  $3 \times 10^{-7}$  or less result in mutagenesis induced by triple helix formation. Since  $2 \times 10^{-7}$  is obviously less than  $3 \times 10^{-7}$ , dissociation constants of less than or equal to  $2 \times 10^{-7}$  are supported by the '376 patent.

Furthermore, the '376 patent at least at column 5, lines 7-35, provide methods for determining a  $K_d$  of less than or equal to  $2 \times 10^{-7}$  for an oligonucleotide/target pair. Therefore, claims 7-12 and 25 are supported by the '326 and '476 patents.

The Examiner argues that the '376 and '426 patents do not support the concept of a TFO having a length between 10 and 60 nucleotides as defined by claim 8. As discussed above, TFOs were well known in the art and a patent should preferably omit what is well known in the art. The '376 and '426 patents discloses exemplary suitable TFOs of 7 to 40 nucleotides (see column 4, line 4 of the '376 patent) and TFOs of 10, 20, 30 and 57 nucleotides in length. This clearly demonstrates that the Appellant had conceived that TFOs of different lengths were suitable for use in the methods defined by the claims and demonstrates TFOs of between 10 to 60 nucleotides in length as defined in claim 8 is supported by the '376 and '426 patents.

The Examiner also alleges that the '376 and '426 patents do not support conception of a TFO that is tethered or untethered to a donor nucleic acid. Based on the level of knowledge in

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the art, one of skill in the art would have recognized that a TFO and donor nucleic acid can be used in a tethered or untethered manner based on the disclosure of the '376 and '426 patents. At least at the paragraph spanning column 1 to column 2, the '376 patent discloses that TFOs are useful *alone or linked to reactive moieties*. The '376 patent at least at column 3, lines 49-56, describes methods for using TFOs to stimulate recombination of a DNA fragment into a target region. Furthermore, the '376 patent discloses at least at column 6, lines 40-58, that a triplex forming oligonucleotide can be administered to a cell *in combination with a separate DNA fragment*. The '376 patent also describes co-administration of a triplex forming oligonucleotide *with the recombination fragment*. Oligonucleotides were routinely chemically synthesized by commercial suppliers as of the priority date of the present application. If one of skill in the art wanted a TFO tethered to a donor nucleic acid, all one had to do was order its synthesis from a commercial supplier as was done in the present application (see page 17, lines 19-26). Clearly these molecules can also be synthesized separately. The '376 patent describes chemical synthesis of oligonucleotides at least at column 7, lines 34-58. Furthermore, methods for linking strands of DNA (e.g., generating a recombinant plasmid) were well known to one of ordinary skill in the art as of the priority date of the present application. It is clear that the concept of using TFOs tethered or untethered to a donor nucleic acid would be obvious to one of skill in the art based on the level of knowledge in the art and the disclosure provided in the '376 and '426 patents. Therefore, the present application is entitled to a priority date of 1995 and Chan is not prior art.

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Based on what was known in the art concerning DNA fragments for use in homologous recombination methods, one of skill in the art could generate donor nucleic acids of any length, especially donor nucleic acids at least 30 nucleotides in length or between 10 and 40 nucleotides in length for use in the methods as defined by the claims of the present application (e.g., via chemical synthesis). As described above, and admitted by the Examiner in the Examiner's Answer (see page 20), the '376 and '426 patents describe the use of TFOs in conjunction with a donor nucleic acid to promote targeted recombination. Therefore, claims 12 and 25 are supported by the disclosure of the '376 and '426 patents.

**(3) SUMMARY AND CONCLUSION**

(1) The specification, in *combination* with information known in the art at the time of filing, clearly enables one skilled in the art to practice the claimed method. Appellant has demonstrated by virtue of the examples that the *in vitro* data is predictive of the *in vivo* results. Appellant has provided results for oligonucleotides linked or unlinked to a donor nucleic acid using both cell-free and cell systems. Absent some evidence otherwise, one skilled in the art would expect the oligonucleotides linked or unlinked to a donor nucleic acid to promote targeted recombination in animals as in the cell systems, based on the evidence in the specification.

(2) Appellant has extensively demonstrated that the claims of the present application are fully supported by the '376 and '426 patents. Therefore, Chan, published in 1999, is not prior art.

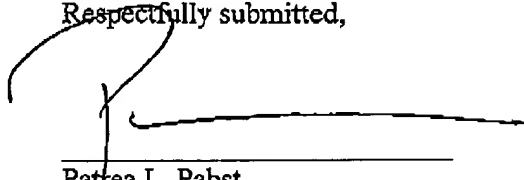
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For the foregoing reasons, Appellant submits that claims 7-12 and 15-25 are patentable.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Patrea L. Pabst', is written over a horizontal line.

Patrea L. Pabst  
Reg. No. 31,284

Date: February 23, 2006

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